Clinical Commentary Review

Hereditary Angioedema with Normal C1-INH (HAE Type III)

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Hereditary angioedema (HAE) with normal C1 inhibitor (C1-INH), also known as HAE type III, is a familial condition only clinically recognized within the past three decades. Similar to HAE from C1-INH deficiency (HAE types I and II), affected individuals experience unpredictable angioedema episodes of the skin, gastrointestinal tract, and airway. Unique clinical features of HAE with normal C1-INH include the predominance of affected women, frequent exacerbation by estrogen, and a prominence of angioedema that involves the face and oropharynx. The underlying pathophysiology of HAE with normal C1-INH is poorly understood, but indirect evidence points to contact pathway dysregulation with bradykinin-mediated angioedema. Currently, evaluation is complicated by a lack of confirmatory laboratory testing such that clinical criteria must often be used to make the diagnosis of HAE with normal C1-INH. Factor XII mutations have been identified in only a minority of persons affected by HAE with normal C1-INH, limiting the utility of such analysis. To date, no controlled clinical studies have examined the efficacy of therapeutic agents for HAE with normal C1-INH, although published evidence supports frequent clinical benefit with medications shown effective in HAE due to C1-INH deficiency. **(J Allergy Clin Immunol: In Practice 2013;■:■-■)**

Key words: *Hereditary angioedema; normal C1-INH; type III; estrogen; diagnosis; treatment; factor XII mutation*

Angioedema is among the most common symptoms presenting to the allergy-immunology specialist and requiring emergency medical care or hospitalization.[1-4] Although most patients presenting with acute or recurring angioedema episodes have histamine-mediated symptoms, a subset of persons experience nonhistaminergic swelling that is unresponsive to antihistamine and corticosteroid therapy.[5] In recent years, hereditary angioedema (HAE) due to C1 inhibitor (C1-INH) deficiency (HAE types I and II, denoted in this review as HAE−C1-INHdef) has received increased attention because of improved understanding of the pathophysiology and a resultant influx of clinical research aimed at developing new therapies for this condition.[6-8] These advances have dramatically altered the treatment paradigm for patients deficient of C1-INH.[9-12] Perhaps partially because of educational efforts, awareness, and diagnostic testing for C1-INH deficiency, clinicians have identified a subset of patients with familial nonhistaminergic angioedema but normal C1-INH levels and function. This article reviews the clinical characteristics, putative pathophysiology, diagnostic criteria, and treatment considerations for HAE with normal C1-INH (HAE−nmlC1-INH).

HAE−nmlC1-INH (frequently called *HAE type III*) was clinically recognized by clinician-investigators in the 1980s. Subsequently, Bork et al[13] published a complete clinical description of this observed patient cohort in 2000. Bork et al[13] described 10 female patients with recurrent cutaneous, intestinal, and airway angioedema symptoms remarkably similar to HAE−C1-INHdef, but with normal C1-INH level and function. Importantly, all 10 of these women had a positive family history of a direct relative with similar symptomatology. In total, an additional 26 affected persons were identified within the families of the original 10 index patients. Concurrently in 2000, Binkley et al[14] characterized an inherited form of "estrogen-dependent" angioedema with normal C1-INH levels, now widely recognized to be an additional description of HAE−nmlC1-INH. Subsequent to these original reports, several groups worldwide have published similar cohorts to describe HAE−nmlC1-INH.[15-23] However, limited progress has been made in delineating the underlying pathophysiology or in developing clear diagnostic or management parameters for HAE−nmlC1-INH.

CLINICAL CHARACTERISTICS AND EPIDEMIOLOGY

Important clinical features observed in persons affected by HAE−nmlC1-INH are listed in Table I. The clinical manifestations of HAE−nmlC1-INH are in many respects similar to HAE−C1-INHdef with prominent recurrent angioedema in the absence of associated urticaria.[24] Swelling may involve the tongue, upper airway, extremities, or gastrointestinal tract, although patients with HAE−nmlC1-INH appear to have more frequent facial and oropharyngeal angioedema and less frequent gastrointestinal angioedema than persons with HAE−C1-INHdef. Fatal asphyxiation has been reported in patients with HAE−nmlC1-INH, highlighting the serious nature of angioedema episodes.[25] Swelling episodes typically last 2 to 5 days if untreated. The frequency and severity of angioedema episodes is highly variable, both between affected persons and over time in an individual patient. Notably, HAE−nmlC1-INH generally has a later age of symptom onset than HAE−C1-INHdef, with 92% of patients experiencing

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Abbreviations used
ACE- Angiotensin-converting enzyme
C1-INH- C1 inhibitor
HAE- Hereditary angioedema
HAE−C1-INHdef- Hereditary angioedema due to C1 inhibitor deficiency
HAE−nmlC1-INH- Hereditary angioedema with normal C1 inhibitor
HRT- Hormone replacement therapy
OCP- Oral contraceptive pill

first symptoms during or after the second decade of life.[24] In contrast, >50% of patients with HAE−C1-INHdef experience onset of angioedema symptoms before the age of 10 years.[26] Persons with HAE−nmlC1-INH may experience long symptom-free intervals between episodes, and the proportion of patients presenting with recurrent attacks at a single anatomical location is higher than observed in HAE−C1-INHdef. Prodromal symptoms may occur, although erythema marginatum has not been reported in HAE−nmlC1-INH. Patients may develop hemorrhaging into areas of angioedema, a finding that appears unique to this HAE subtype.[24] Importantly, the angioedema symptoms of HAE−nmlC1-INH are refractory to acute or preventative treatment with systemic antihistamines and corticosteroids.

HAE−nmlC1-INH predominantly affects women with only a small number of affected male patients described.[21,23,25] As the terminology suggests, HAE−nmlC1-INH is defined as a familial disease, with the original published descriptions requiring the criterion of affected family members with similar angioedema symptoms. Sporadic or *de novo* cases of HAE−nmlC1-INH are an area of some controversy, given the current substantial reliance on clinical diagnosis and the lack of a reliable diagnostic biomarker in most cases (see Diagnosis section). Currently, HAE−nmlC1-INH is believed to be rare with <300 published cases. However, current diagnostic limitations make accurate prevalence estimates difficult.

Because affected persons are predominantly female, it is hypothesized that phenotypic expression is strongly affected by hormonal influences. Specifically, estrogen appears to be an important cofactor or trigger in symptom manifestations.[27] This is supported by the observation of increased angioedema activity concurrent with high-estrogen states (estrogen-containing medication use, pregnancy, etc).[21,23] Patient surveys in women with HAE−nmlC1-INH have indicated this exacerbating influence of oral contraceptive pills (OCPs), pregnancies, and hormone replacement therapies (HRTs) on symptoms.[28] Of 27 affected women who received estrogen-containing OCPs, 17 (63%) reported that their first clinical symptoms of angioedema occurred with the initiation of an estrogen-containing OCP. An additional eight women (30%) reported angioedema symptoms worsening with use of OCPs, and two (7%) reported no symptom change with OCP use. Of the 25 women who experienced pregnancy, 3 (12%) reported their first angioedema symptoms after pregnancy, 7 (28%) reported worsening of existing symptoms, 10 (40%) reported no symptom change, and 5 (20%) reported symptom improvement.[6] Of the seven women receiving estrogen-containing HRT, three (43%) reported worsening of existing symptoms, and four (57%) reported no change. In an additional study of 39 women with HAE−nmlC1-INH, 62% reported clinical symptoms were either induced or worsened by estrogen-containing OCPs or HRT.[29] Clearly, the detrimental effect of estrogen on angioedema symptoms is recognized as a common feature, but it is highly variable between affected persons.

TABLE I. Major clinical features of HAE with normal C1-INH

Age of symptom onset	Typically adulthood; mean age 27 ±14 y[26]
Sex	Predominantly female
Anatomical location of angioedema symptoms	Prominence of facial, tongue, oropharyngeal symptoms Gastrointestinal symptoms in approximately 50% of patients Multiorgan attacks uncommon
Prodromal symptoms	May occur although lack of erythema marginatum
Inheritance pattern	Autosomal dominant with frequent low penetrance; obligate asymptomatic carrier possible
Exacerbating factors	Estrogen exacerbates in most but not all cases
Treatment response	Antihistamines and corticosteroids ineffective Reports of variable efficacy for the following: - Acute therapy with C1-INH, icatibant, ecallantide - Prophylactic therapy with progesterone, tranexamic acid, danazol, C1-INH

Similar to HAE−C1-INHdef, other specific triggers have been associated with angioedema episodes in patients with HAE−nmlC1-INH. In a series of 35 patients, the most common triggers of angioedema attacks included acute trauma to the affected area, physical pressure on the affected area, and dental procedures that induced facial and/or tongue swelling. Some patients also reported emotional stress and ingestion of various spices and herbs as suspected triggers, the latter specific to abdominal angioedema attacks.[28]

PATHOPHYSIOLOGY

The causative pathophysiology of HAE−nmlC1-INH is currently unknown. Underlying dysregulation of the contact (plasma kallikrein-bradykinin) system is strongly suspected because of several pieces of indirect evidence. HAE−nmlC1-INH symptoms are markedly similar to C1-INH deficiency, and the absence of urticaria and lack of symptom response to corticosteroid/antihistamine therapy support a nonhistaminergic process. Estrogen is known to upregulate activation of the kallikrein-bradykinin system[30,31] and is recognized to worsen the disease manifestations not only in patients with HAE−nmlC1-INH but also in patients with HAE−C1-INHdef in whom dysregulated bradykinin production is firmly established as the underlying pathophysiology.[32-34] Likewise, angiotensin-converting enzyme (ACE) inhibitors can exacerbate attack frequency and severity in HAE−nmlC1-INH, presumably by preventing bradykinin degradation.[35] Finally, HAE−nmlC1-INH clinical symptoms have been observed to respond to medications targeted at reducing the production of and/or biologic effects of bradykinin (see Treatment Considerations section). Despite this

evidence, the contact system hypothesis for HAE−nmlC1-INH has not been definitively proven.

Given that C1-INH protein level and function have been shown to be normal in this patient population, preliminary investigations have focused on other potential points of dysregulation within the contact system.[36] In addition, on the basis of observed HAE−nmlC1-INH family pedigrees, genetic mutation(s) with an autosomal dominant-variable penetrance pattern have been strongly suspected. A subgroup of persons with HAE−nmlC1-INH has been identified as having mutations of the gene that encodes factor XII (Hageman factor) of the coagulation system.[28,37] Two distinct missense mutations have been described, resulting in threonine-to-lysine (Thr309Lys) and threonine-to-arginine (Thr309Arg) substitutions.[38] Both show inheritance in an autosomal dominant pattern with incomplete penetrance. A third described mutation involves a 72-base pair deletion in the same gene region as the missense threonine substitutions.[37]

The discovery of factor XII mutations in a subset of the HAE−nmlC1-INH population led to a postulated causative mechanism for angioedema symptoms; that is, a putative gain of function of the coagulation factor conferred by the mutations leading to upregulation of contact system activation and increased bradykinin release.[39] However, a subsequent study aimed at verifying this mechanism failed to find enhanced activation of the factor XII-prekallekrein-bradykinin−forming cascade.[40] Thus, current mechanistic data are conflicting, and the importance of factor XII mutations in the pathogenesis of this condition is unclear. Notably, the described factor XII mutations appear more prevalent in the European HAE−nmlC1-INH population, with such mutations identified in up to 25% of cohorts.[28] In the United States, factor XII mutations have been exceedingly rare in the population tested for suspected HAE−nmlC1-INH.[41] To date, it appears that factor XII mutations are a potentially useful biomarker for HAE−nmlC1-INH in only a minority of the affected population with regional differences influenced strongly by a founder effect. On the basis of these findings, HAE−nmlC1-INH can be categorized into subtypes of HAE−nmlC1-INH−factor XII mutation and HAE−nmlC1-INH−unknown. The presence of factor XII mutation(s) has not been associated with any clear phenotypic differences. Other potential contributory genetic polymorphisms in bradykinin degradation enzymes aminopeptidase P and angiotensin converting-enzyme have been described in a few patients with HAE−nmlC1-INH.[42] The relevance of these polymorphisms to clinical phenotype is unknown.

Of additional interest, although reported in only a subset of a single cohort of patients with HAE−nmlC1-INH−factor XII mutation, is the finding that C1-INH function dropped to <50% during five studied angioedema attacks.[23] This may suggest consumption of C1-INH by activation of enzymes in the contact or complement system during swelling episodes. This finding has yet to be replicated in other cohorts with HAE−nmlC1-INH although other groups have reported modest decreases in C1-INH function (<70%) during periods of high estrogen exposure in some patients.[21,28]

The observation that most patients with HAE−nmlC1-INH are females first developing symptoms after puberty suggests a potential role of estrogen in disease pathogenesis. This concept of estrogen-sensitive or estrogen-dependent angioedema is supported by the aforementioned exacerbation of HAE−nmlC1-INH symptoms during elevated estrogen states due to exogenous (OCP, HRT) or endogenous (pregnancy) sources. Estrogen has been shown to increase factor XII levels and to decrease C1-INH levels,[43] as well as to depress aminopeptidase P and ACE, which are important in bradykinin degradation.[27] This might explain increased bradykinin levels in the presence of contact system activation. However, the initiation of symptoms in a few prepubescent females, persistence of disease after menopause, and presence of disease identified in rare males[44] all suggest that HAE−nmlC1-INH is not estrogen dependent per se, but rather that the hormone is a strong cofactor for phenotype expression.

DIAGNOSIS

The diagnosis of HAE−nmlC1-INH is currently challenging due to the lack of a validated confirmative diagnostic test. The condition should be included in the differential diagnosis of any patient presenting with isolated, recurring angioedema in the absence of urticaria. Important clinical clues include duration of symptoms (typically 2-5 days), lack of responsiveness to high-dose systemic antihistamines and corticosteroids, and the historical pattern of cutaneous angioedema and unexplained abdominal pain. Female sex, exacerbation by estrogen, and predilection for the face and oropharynx should increase the clinical suspicion. C1-INH deficiency should be excluded in such patients with a screening C4 level followed by C1-INH level and function if suspicion is high.[45] Evaluation for other underlying causes of recurring angioedema should be performed as suggested by the initial history and physical examination, with diagnostic testing for other systemic or inflammatory causes as appropriate. In patients in whom C1-INH assays are normal, at present, no clinical laboratory testing or biomarker is available to definitively identify or exclude the diagnosis of HAE−nmlC1-INH. Factor XII mutation analysis may be useful; if positive in a person with suggestive clinical symptoms, this finding is strong supportive evidence of HAE−nmlC1-INH. However, on the basis of current data, most patients affected by HAE−nmlC1-INH lack factor XII mutations.

At present the diagnosis of HAE−nmlC1-INH is most often made on the basis of clinical criteria. Recently, an international consensus group published recommended diagnostic criteria for HAE−nmlC1-INH (Table II).[46] It is important to note that these criteria require either an identified factor XII mutation *or* a positive family history of nonhistaminergic angioedema to establish the diagnosis. In addition to fulfillment of these specific criteria, factors worth noting include estrogen exacerbation, as well as anatomical location and severity of angioedema symptoms. Specifically, angioedema due to HAE−nmlC1-INH frequently affects the face or airway with protracted (2-5 days) and sometimes severe swelling that requires airway management due to risk of asphyxiation.[24]

The proposed diagnostic criteria for HAE−nmlC1-INH have clear limitations. At present, no method is definitive for distinguishing HAE−nmlC1-INH from idiopathic, bradykinin-mediated angioedema.[47] The required family history of angioedema in the absence of an identifiable factor XII mutation attempts to distinguish between HAE−nmlC1-INH and sporadic idiopathic bradykinin-mediated angioedema. However, it is plausible that idiopathic bradykinin-mediated angioedema could affect more than one member of a given

TABLE II. Recommended diagnostic criteria for HAE with normal C1-INH[46]

- A history of recurrent angioedema in the absence of concomitant hives or concomitant use of a medication known to cause angioedema
- Documented normal or near normal C4, C1-INH antigen, and C1-INH function
- *Plus one* of the following:
  - Demonstration of a factor XII mutation associated with the disease
  - A positive family history of angioedema *and* documented evidence of lack of efficacy of chronic high-dose antihistamine therapy (cetirizine at 40 mg/d or the equivalent, for at least 1 month and an interval expected to be associated with three or more attacks of angioedema)

family. Furthermore, *de novo* unidentified mutations most certainly occur such that persons with HAE−nmlC1-INH may be the index case in their family, with the familial inheritance pattern only becoming evident in subsequent generations. Finally, the elicited family history of angioedema may be unreliable and subject to recall bias for patients seeking a diagnosis. As such, the current clinical criteria used to identify HAE−nmlC1-INH are imperfect and could infrequently misclassify patients with angioedema. However, until a reliable diagnostic assay or biomarker is validated, these recommended criteria represent the current state of the art for diagnosing HAE−nmlC1-INH. After the clinical diagnosis, successful treatment with a kallikrein-bradykinin−targeted drug (see Treatment Considerations section) may provide additional supportive diagnostic data, although treatment response will not distinguish hereditary from idiopathic forms of bradykinin-mediated swelling.[48] Continued research is necessary to identify objective laboratory data useful in characterizing persons with HAE−nmlC1-INH.

TREATMENT CONSIDERATIONS

HAE−nmlC1-INH symptoms may be debilitating and/or life threatening, depending on the anatomical location, severity, and frequency of the angioedema episodes. Although some triggers exist, the unpredictable nature of the swelling necessitates an established acute management plan, particularly to ensure patient safety in the event of airway involvement. Patients should be advised to avoid known HAE triggers such as exogenous estrogen therapy and ACE inhibitors. Physical trauma, either accidental or iatrogenic (dental/surgical procedures) may trigger swelling episodes.

The medical management of HAE−nmlC1-INH presents clinical challenges because of an absence of controlled investigations of acute or preventative treatment approaches for angioedema associated with this condition. Descriptive clinical cohorts have shown that treatments effective for allergic or histamine-mediated angioedema (H1/H2 antagonists and corticosteroids) are ineffective in HAE−nmlC1-INH.[25] Airway management may be necessary because of the potential risk of asphyxiation with progressive angioedema of the face or upper airway, and symptomatic treatment of abdominal pain may be required. However, to terminate angioedema attacks, recent interventions have focused on the rational therapeutic approach of using medications proven effective for HAE−C1-INHdef, given the remarkable clinical similarities and suspected common pathologic mediators in these conditions.[49]

Although definitive direct proof is lacking for bradykinin as the causative mediator in HAE−nmlC1-INH, the aforementioned indirect evidence supports this hypothesis. Accordingly, published case reports and series identify treatment directed at preventing contact pathway activation and bradykinin effects as beneficial for HAE−nmlC1-INH angioedema. Although published experience is limited, the bradykinin B2 receptor antagonist icatibant has reported efficacy for the treatment of acute symptoms in several patients.[23,50,51] Ecallantide has also been reported successful in treating an angioedema attack in one patient with HAE−nmlC1-INH.[52] Interestingly, despite normal measured C1-INH quantity and function, the use of plasma-derived human C1-INH during acute attacks has been reported effective in many cases when this therapy was attempted, although reports of inefficacy also exist.[21,23,28,53] For long-term prophylaxis, progesterone, danazol and tranexamic acid have been used to treat HAE−nmlC1-INH with variable success. Progesterone has reported efficacy in several published cases, including a recent report of 19 patients with HAE−nmlC1-INH; total or partial reduction in angioedema events was evident in 10 of 13 patients (77%) treated with progestin-only contraceptives, and 13 of 15 patients (87%) treated with higher dose antigonadotropic progestin agents.[54] Effective prevention of attacks with danazol has been reported, although some patients failed to improve.[13,16,55] Tranexamic acid also has reported efficacy for prophylaxis, with the greatest efficacy reported in a French cohort of 26 patients whom all reported at least 50% reduction in frequency or severity of attacks with tranexamic acid 1 g three times daily.[21] Rarely, C1-INH concentrate has been used for short- or long-term prophylaxis with reported success.[21,56] Short-term prophylactic strategies (C1-INH concentrate, attenuated androgens) used to prevent angioedema during medical or surgical procedures in HAE−C1-INHdef have not been studied in HAE−nmlC1-INH.

FUTURE DIRECTIONS

Additional research is needed to better characterize, diagnose, and treat individuals with HAE−nmlC1-INH. With the current poor understanding of the underlying pathophysiology, laboratory efforts to identify the pathway and dysregulation leading to angioedema symptoms will be vitally important. Although it is appears likely that contact system aberrations are responsible for the episodic symptoms of HAE−nmlC1-INH, delineating the specific point(s) of dysregulation will likely provide diagnostic enzyme or mediator assays useful for clinical care. This may also provide direction for the pursuit of additional genetic markers useful in understanding the inheritance risks of the condition. Alternatively, as seen with associated factor XII mutations, gene-based investigations may suggest underlying mechanisms for swelling. Understanding the mechanistic pathway will be critical in guiding the future use of medications both for individual patient care and in facilitating controlled studies to establish therapeutic efficacy and safety profiles for the treatment of HAE−nmlC1-INH. Finally, advances in biomarkers within this patient group will have broader applications to angioedema conditions in general, because the current approach to idiopathic angioedema consists of empirical therapeutic trials that are frequently inefficient and cumbersome. Diagnostic assays that differentiate between

histamine-mediated and bradykinin-mediated symptoms will represent a major advance in managing the broader population of patients who experience debilitating and life-threatening angioedema.

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